

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of : Attorney Docket No. 2006_1315A
Hiroyuki KAMIYA et al. : **Confirmation No. 9531**
Serial No. 10/588,792 : Group Art Unit 1637
Filed October 26, 2006 : Examiner Suchira Pande
METHOD OF CONVERTING BASE IN DNA : **Mail Stop: AF**
SEQUENCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants respectfully request review of the Examiner's position, as set forth in the final Office Action dated February 16, 2011, and the Advisory Action dated June 1, 2011.

No amendments are being filed with this request.

This request is being filed together with a Notice of Appeal, and the required fees.

The review is requested for the reasons set forth on the attached sheets, of which there are no more than five.

Respectfully submitted,

Hiroyuki KAMIYA et al.

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Reasons for Review

Applicants assert that the rejection of record is not proper, and is without basis, for the reasons described below. Specifically, there are clear legal and factual deficiencies in the rejection, which render the rejection untenable.

Applicants' claim 12 is directed towards an *in vitro* base conversion method of a DNA sequence, which is a method of converting one or more bases in a target DNA sequence in a cell, consisting of preparing a single-stranded DNA fragment having 300 to 3,000 bases by cleavage from a single-stranded circular DNA, and introducing said single-stranded DNA fragment into a cell, wherein said single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence, and contains the base(s) to be converted. The other pending claims under examination are dependent upon this claim.

In the final Office Action of February 16, 2011, the Examiner asserts that Zarling in view of Moriya teaches:

- (1) Zarling et al. teaches an *in vitro* base conversion method of a cDNA sequence, which is a method of converting one or more bases in a target DNA sequence in a cell, but Zarling et al. does not teach preparing a single-stranded DNA fragment by cleavage from a single-stranded circular DNA;
- (2) Moriya teaches use of shuttle phagemid vectors for production of single stranded DNA. One of ordinary skill in the art knows that shuttle phagemid vectors have architecture that allows one to express the desired (+ sense strand) or (- antisense strand) strand. So 100% of the DNA produced as single stranded DNA can be the desired sense or antisense strand.
- (3) If one desires to have 100% population containing only either the + or - strand, then the target gene of appropriate fragment size can be cloned in the multiple cloning site of the chosen phagemid vector.

Applicants respectfully question the Examiner's assertion above in part (3). The Examiner has not provided motivation to produce a population containing either only the + or - strand for base conversion method. Zarling et al. describes that a mixture of + and - strands prepared from PCR products can be effective for base conversion of a target gene. How would one of skill in the art know that only the + or - strand would be more effective?

In response, the Examiner set forth reasoning as follows in the Advisory Action of June 1, 2011:

One of ordinary skill in the art knows that shuttle phagemid vectors have architecture that allows one to express the desired (+sense strand) or (-antisense strand) strand. So 100% of the DNA produced as single stranded DNA is the desired sense or antisense strand. The target gene of appropriate fragment size can be cloned in the multiple cloning site of the chosen appropriate phagemid vector. These phagemid clones can be used to produce single stranded circular DNA of desired sense. Moriya teaches how desired fragment can be cleaved from this single stranded DNA. In this case 100% of the single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence, and contains the base(s) to be converted.

One of ordinary skill in the art also has a reasonable expectation that by practicing the method of Moriya in the method of Zarling et al. i.e. by cloning desired target in the phagemid taught by Moriya, one of ordinary skill in the art would be able to prepare desired (DNA fragment that is homologous with a sense strand of the target strand) single stranded DNA fragment. This single stranded DNA fragment obtained can be transfected into desired host cells to successfully perform targeted homologous recombination".

However, the Examiner has failed to provide a technical reason or motivation to combine the references. Instead, the Examiner has merely noted that it is possible to use single strand DNA to prepare a desired fragment. Why a skilled artisan would perform such extra steps, without use of impermissible hindsight in view of the claimed invention, is absent from the Examiner's statement.

In the Advisory Action, the Examiner further indicates that the 10 fold improvement in conversion efficiency shown on page 25 of the specification using the claimed method is obvious for the following reasons:

Examiner maintains the previous position and would like to point out that conversion efficiency depends on several factors such as cells being used for conversion, length of the fragment and other conditions used for transformation. The instant claims do not recite any particular conditions, nor do they recite conversion efficiency, hence arguments regarding conversion efficiency are not commensurate with the scope of the claimed invention.

Applicants respectfully disagree. The results shown in the specification indicate a **10 fold** increase in conversion efficiency, the only significant difference being the use of a single stranded DNA. It is technically unlikely that this increase in conversion efficiency is due to other factors. It is also unlikely that a person of skill in the art would fail to realize the increase in efficiency with mere routine changes in the transformation conditions. The Examiner has failed to back up the assertion that routine changes would result in the loss of conversion efficiency with any evidence.

The concept of the claimed invention is that use of the single-stranded *sense* DNA enhances the efficiency of base conversion of a target gene in a cell. This inventive concept is not disclosed or suggested in Zarling et al. There is no motivation for one of in the art of base conversion to produce only + or - strand DNA fragment from phagemid vector.

Applicants furthermore refer to MPEP 2142:

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).

Applicants respectfully suggest that the Examiner has merely shown that plus or minus strains can be made but has not articulated reasoning with some rational underpinning to support combination of single strain sense DNA fragment with the teachings of Zarling.

The Examiner also rejects the applicants' arguments as to superior conversion efficiency of the invention, because the instant claims do not recite any particular conditions that affect efficiency of conversion. However, Applicants note that use of a sense-stranded DNA fragment inherently has superior efficiency compared with other DNA fragment(s). Examples in the present application compare base conversion efficiencies of the following DNA fragments under the same conditions:

- (a) single-stranded sense DNA fragment (the present invention);
- (b) single-stranded antisense DNA fragment;
- (c) mixture of sense and antisense DNA fragments that are prepared by denaturation of a double-stranded DNA fragment; and
- (d) mixture of sense and antisense DNA fragments that are prepared by denaturation of a PCR product (Zarling et al.).

The examples in the specification show the superior efficiency of single-stranded sense DNA fragment, which does not depend on other conditions. For instance, please see Figs. 3 and 4.

Thus, Applicants respectfully request the Examiner to again consider the evidence of superior conversion efficiency shown in the specification. Such superior conversion efficiency is due to use of single-stranded sense DNA fragment and therefore is recited in the claims. It is superfluous to further indicate in the claims that there is superior conversion efficiency as such is an inherent effect of using single-stranded sense DNA. Furthermore, although the Examiner is

correct that absolute conversion efficiency is affected by numerous variables, the use of single-stranded sense DNA will always result in superior conversion efficiency when compared to other DNA mixtures under the same conditions. The Examiner's contention that manipulation of other variables will result in conversion efficiencies variations lacks evidentiary support. To indicate that the claimed invention does not enhance conversion efficiency by comparison of reactions with different DNA mixtures (single or double stranded) and different reaction conditions is not a true comparison. A person of skill in the art clearly understands that enhance conversion efficiency of the claimed invention refers to comparison of two identical reactions except for the DNA mixture.

Thus, Applicants note that (1) the Examiner has failed to provide an articulated reason for combining the references and (2) the Examiner has failed to consider that the use of single-stranded sense DNA greatly enhances efficiency of base conversion.

For the reasons articulated above, there are clear legal and factual deficiencies in the rejection, which render the rejection unsound. Reversal of the outstanding rejection is respectfully requested